WEST

Generate Collection | Print

L3: Entry 1 of 43 File: USPT Mar 4, 2003

DOCUMENT-IDENTIFIER: US 6527759 B1
TITLE: Ultrasound assembly for use with light activated drugs

Priority Application Year (1):
1995

Brief Summary Text (28):
A microbubble is also disclosed. The microbubble includes a substrate defining a shell of the microbubble and having a thickness permitting hydraulic transport of the microbubble. The microbubble also includes a light activated drug activatable upon exposure to ultrasound energy. Activation of the light activated drug causes a disruption in the shell sufficient to cause a rupture of the microbubble. The microbubble further includes a therapeutic releasable from the microbubble upon rupture of the microbubble and yielding a therapeutic effect upon release from the microbubble.

Detailed Description Text (10):
In one preferred embodiment, the light activated drug includes an oligonucleotide acting as a site specific molecule coupled with a texaphyrin. The oligonucleotide can have an affinity for a targeted site on a DNA strand. For instance, the oligonucleotide can be designed to have complementary Watson-Crick base pairing with the targeted DNA site. Activation of the light activated drug after the conjugate has bound the targeted DNA site can cause cleavage of the DNA strand at the targeted DNA site. As a result, the activated conjugate can be used for cleavage of targeted DNA sites. The light activated conjugate can be targeted to a site on viral DNA where activation of the light activated conjugate causes the virus to be killed. Similarly, the light activated conjugate can be targeted to oncogenes. Other applications of targeted DNA cleavage include, but are not limited to, antisense applications, specific cleavage and subsequent recombination of DNA; destruction of viral DNA; construction of probes for controlling gene expression at the cellular level and for diagnosis; and cleavage of DNA in footprinting analyses, DNA sequencing, chromosome analysis, gene isolation, recombinant DNA manipulations, mapping of large genomes and chromosomes, in chemotherapy and in site directing mutagenesis.

Detailed Description Text (14):
The media can also include microbubbles comprised from a substrate which forms a shell. Suitable substrates for the microbubble include, but are not limited to, biocompatible polymers, albumins, lipids, sugars or other substances. The light activated drug can be enclosed within the microbubble, coupled with the shell and/or distributed in the media outside the microbubble. A preferred microbubble comprises a lipid substrate such as liposome. Systemic administration of liposomes with light activated drug has been shown to result in an increased accumulation and more prolonged retention of light activated drugs within cultured malignant cells and within tumors in vivo. Jori et al., Br. J. Cancer, 48:307-309 (1983); Cozzani et al., In Porphyrins in Tumor Phototherapy, 173-183, Plenum Press (Andreoni et al. eds. 1984). As a result, inclusion of the light activated drug within a liposome combined with the localized delivery of the light activated drug can serve to enhance the localization of the light activated drug within the tissue site.

Detailed Description Text (24):
Other suitable therapeutics include, but are not limited to: thrombolytic agents such as urokinase; coagulants such as thrombin; antineoplastic agents, such as platinum

compounds (e.g., spiroplatin, cisplatin, and carboplatin), methotrexate, adriamycin, taxol, mitomycin, ansamitocin, bleomycin, cytosine arabinoside, arabinosyl adsnine, mercaptopolylysine, vincristine, busulfan, chlorambucil, melphalan (e.g.,PAM, L-PAM or phenylalanine mustard), mercaptopurine, mitotane, procarbazine hydrochloride dactinomycin (actinomycin D), daunorubicinhydrochloride, doxorubicin hydrochloride, mitomycin, plicamycin (mithramycin), aminoglutethimide, estramustine phosphate sodium, flutamide, leuprolide acetate, megestrol acetate, tamoxifen citrate, testolactone, trilostane, amsacrine (m-AMSA), asparaginase (L-asparaginase) Erwinaasparaginase, etoposide (VP-16), interferon alpha -2a, interferon alpha-2b, teniposide (VM-26), vinblastine sulfate (VLB), vincristine sulfate, bleomycin, bleomycin sulfate, methotrexate, adriamycin, and arabinosyl; blood products such as parenteral iron, hemin; biological response modifiers such as muramyldipeptide, muramyltripeptide, microbial cell wall components, lymphokines (e.g.,bacterial endotoxin such as lipopolysaccharide, macrophage activationfactor), sub-units of bacteria (such as Mycobacteria, Corynebacteria), the synthetic dipeptide N-acetyl-muramyl-L-alanyl-D-isoglutamine; anti-fungalagents such as ketoconazole, nystatin, griseofulvin, flucytosine (5-fc), miconazole, amphotericin B, ricin, and beta -lactam antibiotics (e.g.,sulfazecin); hormones such as growth hormone, melanocyte stimulating hormone, estradiol, beclomethasone dipropionate, betamethasone,betamethasone acetate and betamethasone sodium phosphate, vetamethasonedisodiumphosphate, vetamethasone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, flunsolide, hydrocortisone, hydrocortisone acetate, hydrocortisonecypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolonesodium succinate, paramethasone acetate, prednisolone, prednisoloneacetate, prednisolone sodium phosphate, prednisolone rebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide and fludrocortisone acetate; vitamins such ascyanocobalamin neinoic acid, retinoids and derivatives such as retinolpalmitate, and alpha -tocopherol; peptides, such as manganese super oxidedimutase; enzymes such as alkaline phosphatase; anti-allergic agents such as amelexanox; anti-coagulation agents such as phenprocoumon and heparin; circulatory drugs such as propranolol; metabolic potentiators such asglutathione; antituberculars such as para-aminosalicylic acid, isoniazid, capreomycin sulfate cycloserine, ethambutol hydrochloride ethionamide, pyrazinamide, rifampin, and streptomycin sulfate; antivirals such as acyclovir, amantadine azidothymidine (AZT or Zidovudine), Ribavirin andvidarabine monohydrate (adenine arabinoside, ara-A); antianginals such asdiltiazem, nifedipine, verapamil, erythrityl tetranitrate, isosorbidedinitrate, nitroglycerin (glyceryl trinitrate) and pentaerythritoltetranitrate; anticoagulants such as phenprocoumon, heparin; antibiotics such as dapsone, chloramphenicol neomycin, cefaclor, cefadroxil, cephalexin, cephradine erythromycin, clindamycin, lincomycin, amoxicillin, ampicillin, bacampicillin, carbenicillin, dicloxacillin, cyclacillin, picloxacillin, hetacillin, methicillin, nafcillin, oxacillin, penicillin G, penicillin V, ticarcillin rifampin and tetracycline; antiinflammatories such as difunisal, ibuprofen, indomethacin, meclofenamate, mefenamic acid, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tolmetin, aspirin and salicylates; antiprotozoans such as chloroquine, hydroxychloroquine, metronidazole, quinine and meglumine antimonate; antirheumatics such as penicillamine; narcotics such as paregoric; opiates such as codeine, heroin, methadone, morphine and opium; cardiac glycosides such as deslanoside, digitoxin, digoxin, digitalin and digitalis; neuromuscular blockers such as atracurium besylate, gallamine triethiodide, hexafluorenium bromide, metocurine iodide, pancuronium bromide, succinylcholine chloride (suxamethonium chloride), tubocurarine chloride and vecuronium bromide; sedatives (hypnotics) such as amobarbital, amobarbital sodium, aprobarbital, butabarbital sodium, chloral hydrate, ethchlorvynol, ethinamate, flurazepam hydrochloride, glutethimide, methotrimeprazine hydrochloride, methyprylon, midazolam hydrochloride, paraldehyde, pentobarbital, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, talbutal, temazepam and triazolam; local anesthetics such as bupivacaine hydrochloride, chloroprocaine hydrochloride, etidocainehydrochloride, lidocaine hydrochloride, mepivacaine hydrochloride, procainehydrochloride and tetracaine hydrochloride; general anesthetics such asdroperidol, etomidate, fentanyl citrate with droperidol, ketaminehydrochloride, methohexital sodium and thiopental sodium; and radioactive particles or ions such as strontium, iodide rhenium and yttrium.

Detailed Description Text (26):

Other preferred therapeutics include genetic material such as nucleic acids, RNA, and DNA, of either natural or synthetic origin, including recombinant RNA and DNA and antisense RNA and DNA. Types of genetic material that may be used include, for example, genes carried on expression vectors such as plasmids, phagemids, cosmids, yeast artificial chromosomes (YACs), and defective or "helper" viruses, antigene nucleic acids, both single and double stranded RNA and DNA and analogs thereof, such asphosphorothioate and phosphorodithioate oligodeoxynucleotides. Additionally, the genetic material may be combined, for example, with proteins or other polymers.

Detailed Description Text (27):
Examples of genetic therapeutics that may be included in the microbubbles include DNA encoding at least a portion of an HLAgene, DNA encoding at least a portion of dystrophin, DNA encoding at least a portion of CFTR, DNA encoding at least a portion of IL-2, DNA encoding at least a portion of TNF, an antisense oligonucleotide capable of binding the DNA encoding at least a portion of Ras.

Detailed Description Text (28):
DNA encoding certain proteins may be used in the treatment of many different types of diseases. For example, adenosine deaminase may be provided to treat ADA deficiency; tumor necrosis factor and/or interleukin-2 may be provided to treat advanced cancers; HDL receptor may be provided to treat liver disease; thymidine kinase may be provided to treat ovarian cancer, brain tumors, or HIV infection; HLA-B7 may be provided to treat malignant melanoma; interleukin-2 may be provided to treat neuroblastoma, malignant melanoma, or kidney cancer; interleukin-4 may be provided to treat cancer; HIV env may be provided to treat HIV infection; antisense ras/p53 may be provided to treat lung cancer; and Factor VIII may be provided to treat Hemophilia B. See, for example, Science 258, 744-746.

Detailed Description Text (29):
If desired, more than one therapeutic may be included in the media For example, a single microbubble may contain more than one therapeutic or microbubbles containing different therapeutics may be co-administered. By way of example, a monoclonal antibody capable of binding to melanoma antigen and an oligonucleotide encoding at least a portion of IL-2 may be administered in a single microbubble. The phrase "at least a portion of," as used herein, means that the entire gene need not be represented by the oligonucleotide, so long as the portion of the gene represented provides an effective block to gene expression. Further, microbubbles including a therapeutic can be administered before, after, during or intermittently with the administration of microbubbles without a therapeutic. For instance, microbubbles without a therapeutic and microbubbles including a coagulant such as thrombin can be administered to a patient having liver cancer. Activating the light activated drug included with the microbubbles serves to rupture the microbubbles and release the light activated drug and thrombin from the microbubbles. Further activation of the light activated drug can cause tissue death and the thrombin can cause coagulation in and around the damaged tissues.

Detailed Description Text (30):
Prodrugs may be included in the microbubbles, and are included within the ambit of the term therapeutic, as used herein. Prodrugs are well known in the art and include inactive drug precursors which, when exposed to high temperature, metabolizing enzymes, cavitation and/or pressure, in the presence of oxygen or otherwise, or when released from the microbubbles, will form active drugs. Such prodrugs can be activated via the application of ultrasound to the prodrug-containing microbubbles with the resultant cavitation, heating, pressure, and/or release from the microbubbles. Suitable prodrugs will be apparent to those skilled in the art, and are described, for example, in Sinkula et al., J. Pharm. Sci. 1975 64, 181-210, the disclosure of which is hereby incorporated herein by reference in its entirety. Prodrugs, for example, may comprise inactive forms of the active drugs wherein a chemical group is present on the prodrug which renders it inactive and/or confers solubility or some other property to the drug. In this form, the prodrugs are generally inactive, but once the chemical group has been cleaved from the prodrug, by heat, cavitation, pressure, and/or by enzymes in the surrounding environment or otherwise, the active drug is generated. Such prodrugs are well described in the art and comprise a wide variety of drugs bound to chemical groups through bonds such as esters to short, medium or long chain aliphatic carbonates, hemiesters of organic phosphate, pyrophosphate, sulfate, amides,

amino acids, azo bonds, carbamate, phosphamide, glucosiduronate, N-acetylglucosamine and beta-glucoside. Examples of drugs with the parent molecule and the reversible modification or linkage are as follows: convallatoxin with ketals, hydantoin with alkyl esters, chlorphenesin with glycine or alanins esters, acetaminophen with caffeine complex, acetylsalicylic acid with THAM salt, acetylsalicylic acid with acetamidophenyl ester, naloxone with sulfateester, 15-methylprostaglandin F sub 2 with methyl ester, procaine with polyethylene glycol, erythromycin with alkyl esters, clindamycin with alkylesters or phosphate esters, tetracycline with betains salts, 7-acylaminocephalosporins with ring-substituted acyloxybenzyl esters, nandrolone with phenylproprionate decanoate esters, estradiol with enolether acetal, methylprednisolone with acetate esters, testosterone with n-acetylglucosaminide glucosiduronate (trimethylsilyl) ether, cortisol or prednisolone or dexamethasone with 21-phosphate esters. Prodrugs may also be designed as reversible drug derivatives and utilized as modifiers to enhance drug transport to site-specific tissues. Examples of parent molecules with reversible modifications or linkages to influence transport to a site specific tissue and for enhanced therapeutic effect include isocyanate with haloalkyl nitrosurea, testosterone with propionateester, methotrexate (3-5'-dichloromethotrexate) with dialkyl esters, cytosine arabinoside with 5'-acylate, nitrogen mustard (2,2'-dichloro-N-methyldiethylamine), nitrogen mustard with aminomethyltetracycline, nitrogen mustard with cholesterol or estradiol ordehydroepiandrosterone esters and nitrogen mustard with azobenzene. As one skilled in the art would recognize, a particular chemical group to modify a given drug may be selected to influence the partitioning of the drug into either the shell or the interior of the microbubbles. The bond selected to link the chemical group to the drug may be selected to have the desired rate of metabolism, e.g., hydrolysis in the case of ester bonds in the presence of serum esterases after release from the microbubbles. Additionally, the particular chemical group may be selected to influence the biodistribution of the drug employed in the microbubbles, e.g., N,N-bis(2-chloroethyl)-phosphorodiamidicacid with cyclic phosphoramide for ovarian adenocarcinoma. Additionally, the prodrugs employed within the microbubbles may be designed to contain reversible derivatives which are utilized as modifiers of duration of activity to provide, prolong or depot action effects. For example, nicotinic acid may be modified with dextran and carboxymethlydextran esters, streptomycin with alginic acid salt, dihydrostreptomycin with pamoate salt, cytarabine (ara-C) with 5'-adamantoats ester, ara-adenosine (ara-A) with 5-palmirate and 5'-benzoate esters, amphotericin B with methyl esters, testosterone with 17-beta -alkyl esters, estradiol with formate ester, prostaglandin with 2-(4imidazolyl) ethylamine salt, dopamine with amino acid amides, chloramphenicol with mono- and bis(trimethylsilyl) ethers, and cycloguanil with pamoate salt. In this form, a depot or reservoir of long-acting drug may be released in vivo from the prodrug bearing microbubbles. In addition, compounds which are generally thermally labile may be utilized to create toxic free radical compounds. Compounds with azolinkages, peroxides and disulfide linkages which decompose with high temperature are preferred. With this form of prodrug, azo, peroxide or disulfide bond containing compounds are activated by cavitation and/or increased heating caused by the interaction of ultra with the microbubbles to create cascades of free radicals from these prodrugs entrapped therein. A wide variety of drugs or chemicals may constitute these prodrugs, such as azo compounds, the general structure of such compounds being R--N.dbd.N--R, wherein R is a hydrocarbon chain, where the double bond between the two nitrogen atoms may react to create free radical products in vivo. Exemplary drugs or compounds which may be used to create free radical products include azo containing compounds such as azobenzene,2,2'-azobisisobutyronitrile, azodicarbonamide, azolitmin, azomycin, azosemide, azosulfamide, azoxybenzene, aztreonam, sudan III, sulfachrysoidine, sulfamidochrysoidine and sulfasalazine, compounds containing disulfide bonds such as sulbentine, thiamine disulfide, thiolutin, thiram, compounds containing peroxides such as hydrogen peroxide and benzoylperoxide, 2,2'-azobisisobutyronitrile, 2,2'-azobis(2-amidopropane) dihydrochloride, and 2,2'-azobis(2,4dimethylvaleronitrile). A microbubble having oxygen gas on its interior should create extensive free radicals with cavitation. Also, metal ions from the transition series, especially manganese, iron and copper can increase the rate of formation of reactive oxygen intermediates from oxygen. By including metal ions within the microbubbles, the formation of free radicals in vivo can be increased. These metal ions may be incorporated into the microbubbles as freesalts, as complexes, e.g., with EDTA, DTPA, DOTA or desferrioxamine, or asoxides of the metal ions. Additionally, derivatized complexes of the metal ions may be bound to lipid head groups, or

lipophilic complexes of the ions may be incorporated into a lipid bilayer, for example. When exposed to thermal stimulation, e.g., cavitation, these metal ions then will increase the rate of formation of reactive oxygen intermediates. Further, radiosensitizers such as metronidazole and misonidazole may be incorporated into the gas-filled liposomes to create free radicals on thermal stimulation. By way of an example of the use of prodrugs, an acylated chemical group may be bound to a drug via an ester linkage which would readily cleave in vivo by enzymatic action in serum. The acylated prodrug can be included in the microbubble. When the microbubble is ruptured, the prodrug will then be exposed to the serum. The ester linkage is then cleaved by esterases in the serum, thereby generating the drug. Similarly, ultrasound may be utilized not only to activate the light activated drug so as to burst the gas-filled liposome, but also to cause thermal effects which may increase the rate of the chemical cleavage and the release of the active drug from the prodrug. The microbubbles may also be designed so that there is a symmetric or an asymmetric distribution of the therapeutic both inside and outside of the microbubble. The particular chemical structure of the therapeutics may be selected or modified to achieve desired solubility such that the therapeutic may either be encapsulated within the interior of the microbubble or couple with the shell of the microbubble. The shell-bound therapeutic may bear one or more acyl chains such that, when the microbubble is popped or heated or ruptured via cavitation, the acylated therapeutic may then leave the surface and/or the therapeutic may be cleaved from the acyl chains chemical group. Similarly, other therapeutics may be formulated with a hydrophobic group which is aromatic or sterol in structure to incorporate into the surface of the microbubble.

Detailed Description Text (100):
As discussed above, the light activated drug can be coupled with a site directing molecule to form a light activated drug conjugate. Suitable site-directing molecules include, but are not limited to: polydeoxyribonucleotides, oligodeoxyribonucleotides, polyribonucleotide analogs, oligoribonucleotide analogs; polyamides including peptides having an affinity for a biological receptor and proteins such as antibodies; steroids and steroid derivatives; hormones such as estradiol or histamine; hormone mimics such as morphine and further macrocycles such as sapphyrins and rubyrins. It is understood that the terms "nucleotide", "polynucleotide", and "oligonucleotide", as used herein and in the appended claims, refer to both naturally occurring and synthetic nucleotides, poly- and oligonucleotides and to analogs and derivatives thereof such as methylphosphonates, phosphotriesters, phosphorothioates, and phosphoramidates and the like. Deoxyribonucleotides and ribonucleotide analogs are contemplated as site-directing molecules.

L3: Entry 5 of 43 File: USPT Apr 2, 2002

DOCUMENT-IDENTIFIER: US 6365730 B1
TITLE: DNA-Armed ribozymes and minizymes

Priority Application Year (1):
1990

Priority Application Year (2):
1990

Brief Summary Text (3):
Ribozymes are RNA molecules that can cut or ligate other nucleic-acid molecules (usually RNA) in a catalytic fashion (Cech and Bass, 1986; Altman, et al., 1987). The hammerhead ribozyme is one of the best-known ribozymes. It has been studied extensively in isolated chemical systems (Forster and Symons, 1987; Uhlenbeck, 1987; Haseloff and Gerlach, 1988; Jeffries and Symons, 1989; Koizumi, et al., 1988), and used in gene-control studies in living cells (Cotten and Birnstiel, 1989; Cameron and Jennings, 1989; Sarver, et al., 1990; Saxena and Ackerman, 1990; Sioud and Drlica, 1991; Sioud, et al., 1992). A hammerhead ribozyme as defined by Haseloff and Gerlach (Haseloff and Gerlach, 1988) is shown in FIG. 1. It contains two stretches of conserved nucleotides (boxed), a stem-loop structure (bases 18-29) containing helix II, and flanking nucleotides which form double-helices I and III in combination with the substrate.

Brief Summary Text (4):
The instability of ribozymes in living cells is a major concern. One approach taken to protect transcribed ribozymes from nuclease attack in cells has been to embed the ribozyme in a larger, folded structure. Thus, hammerhead ribozymes have been placed next to the anti-codon loop in t-RNA.sup.met (Cotten and Birnstiel, 1989), the 3' untranslated region of the luciferase gene (Cameron and Jennings, 1989), and in a molecule with bacteriophage T7 transcription terminator at its 3' end (Sioud, et al, 1992). These ribozymes appeared to be more stable than the corresponding, unprotected ribozymes; however, in the only comparative study, the stabilized ribozyme did not cleave more target RNA than the shorter-lived ribozyme, indicating that the protecting structure may decrease the specific activity of that ribozyme (Sioud, et al., 1992).

Detailed Description Text (20):
Poly-endonucleases have the potential to act as anti-sense molecules (Helene, C. and J-J Toulme (1990) Biochemica, Biophysica, Acta 1049: 99-125) as well as endonucleases. By "antisense" is meant the formation of a duplex or double stranded sequence as a result of base pairing between complementary bases of a target sequence and an antisense oligonucleotide, which prevents translation of said sequence as a result of duplex formation or the creation of a template for cleavage of the RNA by RNase H, a cellular ribonuclease which acts to cleave the RNA component of hybridized RNA and DNA sequences.

Detailed Description Text (25):
The phosphate moiety of nucleosides is also subject to derivatisation or modifications, which are well known in the art. For example, replacement of oxygen with nitrogen, sulphur or carbon derivatives to respectively give phosphoramidates, phosphorothioates, phosphodithiolates, and phosphonates. Substitutions of oxygen with nitrogen, sulphur of carbon derivatives may be made in bridging or non bridging positions. It has been well established from work involving antisense oligonucleotides

that phosphodiester and phosphorothioate derivatives may efficiently enter cells (particularly when of short length), possibly due to association with a cellular receptor. Methylphosphonates are probably readily taken up by cells by virtue of their electrical neutrality.

Detailed Description Text (34):
The compounds of this invention may be covalently or non-covalently associated with affinity agents such as proteins, antibodies, steroids, hormones, lipids, specific nucleic acid sequences, intercalating molecules (such as acridine derivatives, for example 9-amino acridine) or the like to modify binding affinity for a substrate nucleotide sequence or increase affinity for target cells, or localization in cellular compartments or the like. For example, the compounds of the present invention may be associated with RNA binding peptides or proteins which may assist in bringing the endonuclease into juxtaposition with a target nucleic acid such that hybridization and cleavage of the target sequence may take place. Nucleotide sequences may be incorporated into the 5' and 3' ends of the groups (X).sub.n and (X).sub.n, to increase affinity for substrates. Such additional nucleotide sequences may form triple helices with target sequences (Strobel, et al., 1991) which may enable interaction with intramolecularly folded substrate. Alternatively, modified bases vide supra within the additional nucleotide sequences may be used that will associate with either single stranded or duplex DNA generating base pair, triplet, or quadruplet, interactions with nucleotides in the substrate.

Detailed Description Text (38):
Further, many methods have been developed for introducing cloned eukaryotic DNAs into cultured mammalian cells (Sambrook et al., 1989):

Detailed Description Text (44):
Further, the compound described herein may be used in plants to cleave undesirable mRNA. The appropriate cleavage would lead to phenotypic changes. Phenotypic changes in plant cells or plants may include drought resistance, salinity resistance, resistance to fungal, viral or bacterial infection; modifications of growth characteristics; sterility; fruit production; flowering; senescence; altering oil seed metabolic pathways to increase production; and the like (see Shewmaker et al. U.S. Pat. No. 5,107,065). It is evident that one or more RNA involved in determining phenotype are identified, such RNAs may be inactivated by cleavage utilizing the endonuclease of this invention and thus the phenotype of the plant or plant cell altered. Diseases or infections which may be treated in plants with endonucleases of this invention include fungal infection, bacterial infections (such as Crown-Gall disease) and disease associated with plant viral infection.

Detailed Description Text (46):
Prokaryotic and eukaryotic cell cultures may be phenotypically modified by treatment with endonucleases of this invention. For example, bacterial cultures or yeast cultures involved in production of food components (such as cheese, bread and dairy products) and alcoholic beverage production may be treated so as to modify enzyme content, flavor production, cell growth rate, culture conditions and the like. Eukaryotic and prokaryotic cells in culture may, for example be protected from infection or disease associated with mycoplasma infection, phage infection, fungal infection and the like.

Detailed Description Text (47):
The compounds of this invention may also be used to treat diseases or infection in humans, animals, plants, or prokaryotic or eukaryotic cells. The ability to treat disease or infection is based on the fact that the compounds of this invention are capable of cleaving any RNA which contains a suitable cleavage site, such as defined by the generic cleavage site X'UY', where X' and Y' represent any nucleotide (preferably wherein the cleavage site is GUC) as described previously. Most RNAs will contain one or more suitable cleavages sites.

Detailed Description Text (50):
Further, the targets for the compound may be a viral gene including viral targets such as cytomegalovirus, hepatitis, herpes, HIV, EBV, papilloma virus, rhinovirus, influenza virus, varicella-zoster virus, parainfluenza virus, mumps virus, respiratory syncytial virus, adenovirus, measles virus, rubella virus, human parvovirus,

poliovirus, rotavirus, echovirus, arbovirus, and human T cell leukemia-lymphoma virus.

Detailed Description Text (52):
Therapeutic strategies involving treatment of disease employing compounds of this invention are generally the same as those involved with antisense approaches, such as described in the anti-sense bibliography of (Chrisley, 1991). Particularly, concentrations of compounds utilized, methods and modes of administration, and formulations involved may be the same as those employed for antisense applications.

Detailed Description Text (53):
An "effective amount" as used herein refers to that amount which provides a desired effect in a mammal having a given condition and administration regimen. Compositions comprising effective amounts together with suitable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers useful for therapy. Such compositions are liquids or lyophilized or otherwise dried formulations and include diluents of various buffer content (e.g., Tris-HCL, acetate phosphate), pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), solubilizing agents (e.g., Thimerosal, benzyl alcohol), bulking substances or tonicity modifiers (e.g., lactose, mannitol), covalent attachment of polymers such as polyethylene glycol to the oligonucleotide, complexation with metal ions, or incorporation of the material into or onto particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, polyvinyl pyrrolidone, etc. or into liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts. Such compositions will influence the physical state, solubility, stability, rate of in vivo release, and rate of in vivo clearance of the oligonucleotide. Other ingredients optionally may be added such as antioxidants, e.g., ascorbic acid; low molecular weight (less than about ten residues) polypeptides, i.e., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; amino acids; such as glycine, glutamine acid, aspartic acid, or arginine; chelating agents such as EDTA; and sugar alcohols such as mannitol or sorbitol. Possible sustained release compositions include formulation of lipophilic depots (e.g., fatty acids, waxes, oils). Also comprehended by the invention are particulate compositions coated with polymers (e.g., polyoxamers or polyoxamines) and oligonucleotides coupled to antibodies directed against tissue-specific receptors, ligands or antigens or coupled to ligands of tissue-specific receptors. Further, specific nucleotide sequences may be added to target the oligonucleotides of this invention to the nucleus, cytoplasm or to specific types of cells. Other embodiments of the compositions of the invention incorporate particulate forms protective coatings, protease inhibitors or permeation enhancers for various routes of administration, including parenteral, pulmonary, nasal and oral.

Detailed Description Text (54):
Suitable topical formulations include gels, creams, solutions, emulsions, carbohydrate polymers, biodegradable matrices thereof; vapors, mists, aerosols, or other inhalants. The oligonucleotides may be encapsulated in a wafer, wax, film or solid carrier, including chewing gums. Permeation enhancers to aid in transport to movement across the epithelial layer are also known in the art and include, but are not limited to, dimethyl sulfoxide and glycols.

Detailed Description Text (88):
In summary, cleavage activity of a ribozyme of the Haseloff-Gerlach type can be maintained despite size reduction and replacement of many RNA nucleotides by DNA. One of the three conserved double helices, helix II, is dispensable to formation of the active structure. The minimized ribozyme, or minizyme, is active as a monomer. We think that these minizymes will be useful in future structural and functional studies of catalytic RNA. They should also prove useful in gene-control studies in living cells (Cotten and Birnstiel, 1989; Cameron and Jennings, 1989; Sarver, et al., 1989; Saxena and Ackerman, 1990), where the DNA component should make them more resistant to RNase.

Detailed Description Text (114):
Recently, Taylor et al. (Taylor, et al., 1992) have reported data on a DNA-armed ribozyme that has 6-fold greater catalytic activity than an analogous all-RNA

ribozyme, when targeted against a 28-mer RNA substrate at 55.degree. C. They attributed the difference in effect to the faster rate of dissociation of the cleavage products from the DNA-armed ribozyme. They also investigated the stability of the ribozymes introduced into cells with Lipofectin, and found that the DNA-armed ribozyme survived longer in cells than the all-RNA ribozyme. Our observations, that a DNA-armed ribozyme displays faster rates of cleavage and faster turnover at 30.degree. C. compared to an all-RNA ribozyme, and the observations of Taylor et al. (Taylor, et al., 1992), of increased turnover rates on a different sequence, together imply a general usefulness for these types of molecules.

Detailed Description Text (144):
5. Increased Stability in Cells

Detailed Description Text (145):
There is data that DNA-armed ribozymes are much more stable in cells than all RNA ribozymes (Taylor, et al., 1992).

Detailed Description Text (152):
Chrisley, L. A. (1991) Antisense Research and Development, 1:65-113.

Detailed Description Text (158):
Forster, A. C. & Symons, R. H. (1987) Cell, 50:9-16.

Detailed Description Text (159):
Forster, A. C. & Symons, R. H. (1987) Cell 49:211-220.

Other Reference Publication (42):
Forster et al. (1987) Cell 50:9-16.

# WEST

Generate Collection | Print

**Search Results** - Record(s) 1 through 10 of 43 returned.

1. Document ID: US 6527759 B1

L3: Entry 1 of 43 File: USPT Mar 4, 2003

US-PAT-NO: 6527759
DOCUMENT-IDENTIFIER: US 6527759 B1

TITLE: Ultrasound assembly for use with light activated drugs

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw Desc | Image

2. Document ID: US 6486131 B2

L3: Entry 2 of 43 File: USPT Nov 26, 2002

US-PAT-NO: 6486131
DOCUMENT-IDENTIFIER: US 6486131 B2

TITLE: Cell-cycle regulatory proteins, and uses related thereto

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWMC | Draw Desc | Image

3. Document ID: US 6451603 B1

L3: Entry 3 of 43 File: USPT Sep 17, 2002

US-PAT-NO: 6451603
DOCUMENT-IDENTIFIER: US 6451603 B1

TITLE: Ribozyme nucleic acids and methods of use thereof for controlling viral pathogens

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWMC | Draw Desc | Image

4. Document ID: US 6406900 B1

L3: Entry 4 of 43 File: USPT Jun 18, 2002

US-PAT-NO: 6406900
DOCUMENT-IDENTIFIER: US 6406900 B1

TITLE: Flea protease proteins, nucleic acid molecules and uses thereof

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

5. Document ID: US 6365730 B1

L3: Entry 5 of 43 File: USPT Apr 2, 2002

US-PAT-NO: 6365730
DOCUMENT-IDENTIFIER: US 6365730 B1

TITLE: DNA-Armed ribozymes and minizymes

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

6. Document ID: US 6297041 B1

L3: Entry 6 of 43 File: USPT Oct 2, 2001

US-PAT-NO: 6297041
DOCUMENT-IDENTIFIER: US 6297041 B1

TITLE: MN gene and protein

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

7. Document ID: US 6297004 B1

L3: Entry 7 of 43 File: USPT Oct 2, 2001

US-PAT-NO: 6297004
DOCUMENT-IDENTIFIER: US 6297004 B1

TITLE: Recombinant viruses displaying a nonviral polypeptide on their external surface

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

---

8. Document ID: US 6291650 B1

L3: Entry 8 of 43 File: USPT Sep 18, 2001

US-PAT-NO: 6291650
DOCUMENT-IDENTIFIER: US 6291650 B1

TITLE: Methods for producing members of specific binding pairs

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc
Image

9. Document ID: US 6225447 B1

L3: Entry 9 of 43 File: USPT May 1, 2001

US-PAT-NO: 6225447
DOCUMENT-IDENTIFIER: US 6225447 B1

TITLE: Methods for producing members of specific binding pairs

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc
Image

10. Document ID: US 6225044 B1

L3: Entry 10 of 43 File: USPT May 1, 2001

US-PAT-NO: 6225044
DOCUMENT-IDENTIFIER: US 6225044 B1

TITLE: Method for gene transfer into cells activated from a quiescent state

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc
Image

Generate Collection | Print

| Term | Documents |
|---|---|
| CELL.USPT. | 341026 |
| CELLS.USPT. | 280929 |
| TRANSPORT.USPT. | 230181 |
| TRANSPORTS.USPT. | 28673 |
| (2 AND TRANSPORT AND CELL).USPT. | 43 |
| (L2 AND CELL AND TRANSPORT).USPT. | 43 |

**Display Format:** TI | Change Format

Previous Page Next Page

# WEST

Help | Logout | Interrupt

Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences | Cases

**Search Results -**

| Term | Documents |
|---|---|
| CELL.USPT. | 341026 |
| CELLS.USPT. | 280929 |
| TRANSPORT.USPT. | 230181 |
| TRANSPORTS.USPT. | 28673 |
| (2 AND TRANSPORT AND CELL).USPT. | 43 |
| (L2 AND CELL AND TRANSPORT).USPT. | 43 |

**Database:** US Patents Full-Text Database
US Pre-Grant Publication Full-Text Database
JPO Abstracts Database
EPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

**Search:** L3

Refine Search

Recall Text | Clear

## Search History

**DATE: Tuesday, April 01, 2003** Printable Copy Create Case

| Set Name side by side | Query | Hit Count | Set Name result set |
|---|---|---|---|
| | *DB=USPT; PLUR=YES; OP=ADJ* | | |
| L3 | L2 and cell and transport | 43 | L3 |
| L2 | L1 and antisense | 186 | L2 |
| L1 | @PRAY <= 1995 AND (antibody same oligonucleotide) | 589 | L1 |

END OF SEARCH HISTORY